

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be apparent that certain changes and modifications may be practiced within the scope of the appended claims.

WHAT IS CLAIMED IS:

1. A method for identifying peptides of interest which bind to a preselected receptor molecule, comprising:

5 transforming host cells with a bacteriophage expression vector which comprises an oligonucleotide library of at least about 10^6 members which encode peptides, wherein a library member is joined in reading frame to the 5' region of a nucleotide sequence encoding an outer structural protein of the

10 bacteriophage;

cultivating the transformed cell under conditions suitable for expression and assembly of bacteriophage particles; and

15 selecting bacteriophage particles having the peptides of interest by means of said peptides' affinity for the preselected receptor molecule.

2. The method of claim 1, further comprising the step of determining the nucleotide sequence encoding the peptide of interest in the selected bacteriophage.

20 3. The method of claim 1, wherein the bacteriophage particles encoding the peptide of interest are enriched by repeating the selection step at least once, where the selected bacteriophage are propagated between said selection steps.

25 4. The method of claim 1, where the receptor is bound to a solid phase and the selected bacteriophage particles are separated from the culture.

30

5. The method of claim 4, wherein said receptor molecule is an antibody or binding fragment thereof.

35 6. The method according to claim 1, wherein the outer protein is a bacteriophage coat protein.

7. The method of claim 1, wherein the bacteriophage encoded by the expression vector is a filamentous phage.

8. The method of claim 7, wherein the filamentous bacteriophage is f1, fd, or M13.

9. The method of claim 8, wherein the bacteriophage is fd or a derivative thereof.

10 10. The method of claim 9, wherein the outer bacteriophage protein is a coat protein.

11. The method of claim 10, wherein the coat protein of the fd bacteriophage is pIII.

12. The method of claim 1, wherein the oligonucleotide library comprises a series of codons encoding a random collection of amino acids.

13. The method of claim 12, wherein the codons encoding the collection of amino acids are represented by $(NNK)_x$ or $(NNS)_x$, where N is A, C, G or T, K is G or T, S is G or C, and x is from 5 to at least 8.

14. The method of claim 13, wherein the series of codons encoding the random collection of amino acids of the oligonucleotide library member encodes a hexa-peptide.

15. The method of claim 13, wherein x is at least 8 and up to about 10% of recombinant bacteriophage particles are screened in the selecting step.

16. The method of claim 12, wherein the oligonucleotide library member further encodes at least one spacer residue.

17. The method of claim 16, wherein a spacer residue comprises Gly.

18. The method of claim 17, wherein the spacer comprises Gly-Gly.

19. The method of claim 12, wherein the variable codon region is prepared from a condensation of activated trinucleotides.

5 20. The method of claim 1, wherein the host cells are transformed by electroporation.

21. The method of claim 1, wherein the oligonucleotide library comprises at least about 10^8 members.

10

22. The method of claim 1, wherein the oligonucleotide library members are inserted in the bacteriophage expression vector so that the N-terminus of the processed bacteriophage outer protein is the first residue of the peptide.

15 23. The method of claim 1, wherein the bacteriophage protein is a preprotein which is processed by the host cell to leave the peptide encoded by an oligonucleotide library member exposed at the N-terminus of the mature outer structural protein.

20 24. The method according to claim 23, wherein the peptide comprises spacer amino acid residues are encoded by the oligonucleotide library members between the N-terminus of the mature outer protein and the C-terminus of the peptide.

25 25. A method for identifying peptides of interest which bind to a preselected receptor molecule, comprising:
30 transforming host cells with a bacteriophage expression vector which comprises an oligonucleotide library which encodes peptides, wherein a library member is joined in reading frame with a nucleotide sequence to encode a fusion protein, wherein the library member represents the 5' member of the fusion protein and the 3' member comprises at least a portion of an outer structural protein of the bacteriophage;

cultivating the transformed cell under conditions suitable for expression and assembly of bacteriophage particles; and

5 selecting bacteriophage particles having the peptides of interest by means of said peptides' affinity for the preselected receptor molecule.

26. A composition comprising a peptide produced according to the method of claim 1, 7, 13, 19 or 25.

10

27. The composition of claim 26, wherein the peptide binds an antibody.

15

28. An oligonucleotide library produced according to claims 1, 7, 13, 19 or 25.

20

29. A host cell transformed with a bacteriophage expression vector which comprises an oligonucleotide library member, joined in reading frame to the 5' region of a nucleotide sequence encoding an outer structural protein of the bacteriophage, wherein the library member encodes a peptide of at least about five to twenty-five amino acids.

25

30. The host cell of claim 29, wherein the oligonucleotide library member comprises a series of codons encoding a random collection of from five to eight amino acids.

30

31. The host cell of claim 30, wherein the oligonucleotide library member further comprises a sequence encoding at least about one to five spacer amino acids which are expressed adjacent to the random collection of amino acids.

35

32. A collection of filamentous bacteriophage particles having a peptide on the N-terminus of a coat protein, wherein the peptide is coded for by a oligonucleotide library member from a randomly generated mixture of oligonucleotides.